REMARKS

First, Applicants acknowledge the withdrawal of the previously raised rejections as noted on pages 2-4 of the Office Action, items 4-8. However, even though the Examiner indicates that the rejections under items 10 and 11 on pages 4-8 are "maintained" rejections, Applicants consider these to be new rejections (see lines 1-4 on page 5; and lines 15-18 on page 6). Hence, Applicants point out, for the record, that all previous rejections are understood to be withdrawn, and all rejections raised in the outstanding Office Action are newly raised.

AMENDMENTS

Claim 61 is amended herein to recite that the antibody has "the biological characteristics of monoclonal antibody 2C4 of:
(a) blocking HRG activation of an ErbB hetero-oligomer comprising ErbB2 and ErbB3 or ErbB4; and
(b) binding to the ErbB2 epitope bound by monoclonal antibody 2C4." Support for this recitation can be found on at least page 13, lines 29-36. The amendment of claim 61 is made without acquiescing in any objection or rejection, in order to expedite prosecution.

Claim 63 is added herein which is like claim 1 as pending, except that it recites "an antibody which binds to the ErbB2 epitope bound by monoclonal antibody 2C4". Support for this language can be found on page 15, lines 20-25, for instance.

In that the amendments do not introduce new matter, entry thereof is respectfully requested.

IDSs

Applicants note that they have not received initialed PTO-1449 forms for the following IDSs:
IDS filed 8/29/2000 (citing ref. nos. 1-115), courtesy copies of references hand delivered 6/11/2002
IDS filed 1/24/2001 (citing ref. nos. 116-218), courtesy copies of references hand delivered 6/11/2002
IDS filed 10/30/2001 (citing ref. no. 223), courtesy copies of references hand delivered 6/11/2002
IDS filed 7/17/2002 (citing ref. no. 224) and
IDS filed 2/27/2003 (citing ref. nos. 227-235).
Applicants would appreciate it if the initialed PTO-1449 forms could be returned, indicating consideration of the cited art by the Office. In the event however

that any IDSs or references have been lost by the PTO, Applicants can provide further copies upon request.

SECTION 102 - GREENE *ET AL.*

Claims 1-2, 4-6, 8-9, 12, 16, 20, 27-29, and 61 are rejected under 35 USC Section 102(e) as being anticipated by US Patent No. 5,824,311 (Greene *et al.*) as evidenced by Jardines *et al. Pathobiology* 61(5-6):268-282 (1993) or Earp *et al. Breast Cancer Res and Treatment* 35:115-132 (1995).

Applicants will explain below why each of the rejected independent claims are patentable over the cited art.

Claim 1 concerns a method of treating cancer in a human, wherein the cancer expresses EGFR and ErbB2, comprising administering to the human a therapeutically effective amount of an antibody which binds ErbB2 and blocks binding of monoclonal antibody 2C4 to ErbB2.

Applicants submit that claim 1, and the claims which depend thereon, are patentable over the cited art.

First, Applicants submit that Greene *et al.* doesn't describe therapy of cancer which "expresses EGFR and ErbB2.".

While the Examiner relies on Jardines *et al.* as teaching that "numerous cancers which express ErbB2 inherently co-express, or concurrently overexpress EGFR, and/or the ErbB ligand TGF-alpha," Applicants submit that Jardines *et al.* rather demonstrates how the present rejection fails. In particular, as noted in column 2 on page 278 of Jardines *et al.*, not all breast cancer patients who express EGFR also express ErbB2. In fact, the number of patients who were EGFR-positive, p185-negative, or EGFR-negative, p185-positive (n = 68) exceeded the number of patients who coexpressed the proteins (n = 14). This indicates that the presently claimed method encompasses therapy of a subgroup of patients not described, neither explicitly nor inherently, in Greene *et al.*

Turning now to the Examiner's reliance on Earp *et al.*, Applicants point out that Earp states at page 121 that EGFR "is found to be overexpressed <u>in representatives</u> of virtually every epithelial malignancy" (emphasis added). Greene does not say that the cancer to be treated will express EGFR, nor does he teach therapy of only the "representative" malignancies contemplated by Earp.

This, in conjunction with Jardine's teachings as noted above indicates that the invention herein concerning therapy of cancer which "expresses EGFR and ErbB2" is not described or suggested by Greene.

Moreover, Applicants submit that the antibody used in the method of claim 1 is not taught by Greene *et al.*

Claim 1 herein involves therapy with an antibody which "blocks binding of monoclonal antibody 2C4 to ErbB2." However, the Examiner urges that "absent evidence to the contrary the antibodies of Greene will block the binding of monoclonal antibody to 2C4." So, the Examiner appears to be relying on inherency with respect to the recitation about the antibody blocking binding of 2C4 to ErbB2 receptor in claim 1. Applicants submit that "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient" Hansgirg v. Kemmer, 102 F. 2d 212, 214, 40 USPQ 665, 667 (C.C.P.A. 1939) and *In re Oelrich*, 666 F. 2d 578, 581, 212 USPQ 323, 326 (C.C.P.A. 1981). Indeed, Applicants can demonstrate that not all antibodies that bind ErbB2 can block binding of 2C4 to ErbB2. In particular, Applicants direct the Examiner's attention to Table 1 on page 1555 of Fendly *et al. Cancer Research* 50:1550-1558 (1990), of record, which demonstrates that not all ErbB2 antibodies block binding of monoclonal antibody 2C4 to ErbB2. This table demonstrates that 2C4, 7D3, and 7F3 blocked binding of 2C4 to ErbB2 (MAbs were considered to share an epitope if each blocked binding of the other by 50% or greater in comparison to an irrelevant Mab control), whereas seven other ErbB2 antibodies didn't. This demonstrates that the method herein concerns therapy with a select subgenus of antibodies which block binding of monoclonal antibody 2C4 to ErbB2. There is no information available to indicate that the antibodies in Greene block binding of monoclonal antibody 2C4 to ErbB2.

Hence, Applicants submit that Greene *et al.* fails to anticipate or render obvious the presently claimed invention in that Greene does not describe or suggest an antibody which blocks binding of monoclonal antibody 2C4 to ErbB2, let alone use of that antibody to treat cancer which expresses EGFR and ErbB2 as presently recited in claim 1.

For the reasons elaborated above, Applicants submit that claim 1, and its dependent claims, are patentable over Greene *et al.*

Turning now to independent **claim 27**, this concerns a method of treating cancer in a human, wherein the cancer expresses but does not overexpress ErbB2 receptor, comprising administering to the human a therapeutically effective amount of an antibody which binds to ErbB2 and blocks ligand activation of an ErbB receptor.

Greene *et al.* explains in column 3, lines 55-62 that "In human primary breast cancer amplification of the neu oncogene was found in about 30% of all malignant tumors examined...The neu protooncogene is expressed at low levels in normal human tissues." Greene further emphasizes that his "treatment is an improvement over tumor treatments already in use because the antibodies affect only tumor cells, unlike mammalian cancer tumor treatments currently in use which affect all cells" (column 4, lines 55-59). Hence, Applicants submit that Greene *et al.* effectively ***teaches away*** from the method of claim 27 which entails therapy of a cancer which expresses but "does not overexpress ErbB2 receptor" in humans, since the reference teaches that the treatment therein is for cells with amplified p185, whereas Greene explains that with his method there is no effect on cells which express p185/ErbB2 at low levels.

Claim 27 is further distinguished over Greene in that it entails therapy employing an antibody that "binds to ErbB2 and blocks ligand activation of an ErbB receptor." The present application demonstrates that not all antibodies that bind ErbB2 can also block ligand activation of an ErbB2 receptor. Page 13, lines 16-28. There is nothing in Greene *et al.* to suggest that one select an antibody which blocks ligand activation of an ErbB receptor for therapy of human patients, let alone patients with a cancer which expresses but does not overexpress ErbB2 receptor.

Accordingly, Applicants submit that claim 27, and its dependent claims, are patentable over Greene *et al.*

Applicants will now explain how **claim 61** is patentable over Greene. Claim 61 is amended herein to recite a method of treating cancer in a human, wherein the cancer expresses EGFR and ErbB2, comprising administering to the human a therapeutically effective amount of an antibody which has the biological characteristics of monoclonal antibody 2C4 of: (a) blocking HRG activation of an ErbB hetero-oligomer comprising ErbB2 and ErbB3 or ErbB4; and (b) binding to the ErbB2 epitope bound by monoclonal antibody 2C4.

Applicants have explained above how Greene *et al.* - even when combined with

Jardines *et al.* or Earp *et al.* - fails to disclose or suggest therapy of a cancer which expresses EGFR and ErbB2, a feature of the method claim 61. For at least this reason, Applicants submit that claim 61 is patentable over Greene.

Claim 61 is further distinguished over Greene *et al.* in that it recites administration of an antibody which has the biological characteristics of monoclonal antibody 2C4 of (a) blocking HRG activation of an ErbB hetero-oligomer comprising ErbB2 and ErbB3 or ErbB4; and (b) binding to the ErbB2 epitope bound by monoclonal antibody 2C4. Greene doesn't describe an antibody that blocks HRG activation of an ErbB hetero-oligomer comprising ErbB2 and ErbB3 or ErbB4, or an antibody that binds to the ErbB2 epitope bound by monoclonal antibody 2C4, let alone therapy therewith as in claim 61.

Applicants submit that claim 61, and its dependent claims, are patentable over Greene *et al.*

Reconsideration and withdrawal of the Section 102 rejection based on Greene *et al.* is respectfully requested.

SECTION 102 - ARAKAWA *ET AL.* OR HUDZIAK *ET AL.*

Claims 1-2, 4-6, 8-9, 16, 20, 27-29 and 61 are rejected under 35 USC Section 102(e) as being anticipated by US Patent No. 5,783,186 (Arakawa *et al.*) or US Patent No. 5,725,856 (Hudziak *et al.*) as evidenced by Jardines *et al.* or Earp *et al.*

Applicants will explain below how each of the rejected independent claims is distinguished over the cited art.

Claim 1 herein recites a method of treating cancer in a human, wherein the cancer expresses EGFR and ErbB2, comprising administering to the human a therapeutically effective amount of an antibody which binds ErbB2 and blocks binding of monoclonal antibody 2C4 to ErbB2.

The Examiner relies on Jardines *et al.* to support the proposition that "many ErbB2 positive patients also overexpress EGFR". In reply, Applicants direct the Examiner's attention to column 2 on page 278 where Jardines explains that not all breast cancer patients who express EGFR also express ErbB2. In fact, the number of patients who were EGFR-positive, p185-negative, or EGFR-negative, p185-positive (n = 68) exceeded the number of patients who coexpressed the proteins

(n = 14). This indicates that the presently claimed method encompasses therapy of a subgroup of patients not described, neither explicitly nor inherently, in the cited primary references. Hence, Applicants submit that therapy of cancer which "expresses EGFR and ErbB2" as recited in claim 1 is patentable over the cited art.

With respect to the Examiner's reliance on Earp *et al.*, Applicants point out that Earp states that EGFR "is found to be overexpressed in representatives of virtually every epithelial malignancy" (emphasis added). The cited art does not say that the cancer to be treated will express EGFR and HER2, nor does it describe therapy of only the "representative" malignancies contemplated by Earp. This, in conjunction with Jardine's teachings as noted above indicates that the invention herein concerning therapy of cancer which "expresses EGFR and ErbB2" is patentable over the cited art.

Moreover, claim 1 concerns therapy with an antibody which "blocks binding of monoclonal antibody 2C4 to ErbB2." The preferred embodiment of Hudziak is the 4D5 antibody which doesn't block binding of monoclonal antibody 2C4 to ErbB2 (Table 1 on page 1555 of Fendly *et al. Cancer Research* 50:1550-1558 (1990)). The mAb 74 in Arakawa is described as having a "unique epitope" (column 11, lines 50-51). There is no evidence to indicate that Arakawa's mAb 74 blocks binding of monoclonal antibody 2C4 to ErbB2.

Hence, reconsideration and withdrawal of the rejection in so far as it applies to claim 1, and its dependent claims, is respectfully requested.

Claim 27 concerns a method of treating cancer in a human, wherein the cancer expresses but does not overexpress ErbB2 receptor, comprising administering to the human a therapeutically effective amount of an antibody which binds to ErbB2 and blocks ligand activation of an ErbB receptor.

Arakawa *et al.* ***teaches away*** from therapy of Claim 27, wherein the "cancer expresses but does not overexpress ErbB2 receptor." Arakawa *et al.* instead describes therapy of "cancers characterized by Her2 overexpression" (column 3, lines 12-13; column 5, lines 53-67). Hudziak *et al.* claims a method of treating a patient "having a carcinoma that overexpresses HER2 receptor" (claim 1).

Moreover, the antibody used in the method of 27 is patentable over the cited art. The antibody is one which binds to ErbB2 and blocks ligand activation of an ErbB

receptor. The preferred embodiment of Hudziak is the 4D5 antibody which doesn't block ligand activation of an ErbB receptor as claimed herein, and is specifically excluded by that recitation in claim 27 (see page 13, lines 16-18 of the present application). As to Arakawa, there is nothing to suggest that the mAb 74 in this reference blocks ligand activation of an ErbB receptor as required by claim 27 herein.

Reconsideration and withdrawal of the Section 102 rejection of claim 27, and the claims dependent thereon, is respectfully requested.

Claim 61 is also patentable over the cited art. Claim 61 as amended herein recites a method of treating cancer in a human, wherein the cancer expresses epidermal growth factor receptor (EGFR) and ErbB2, comprising administering to the human a therapeutically effective amount of an antibody which has the biological characteristics of monoclonal antibody 2C4 of: (a) blocking HRG activation of an ErbB hetero-oligomer comprising ErbB2 and ErbB3 or ErbB4; and (b) binding to the ErbB2 epitope bound by monoclonal antibody 2C4.

With respect to the recitation in claim 61 that the cancer expresses EGFR and ErbB2, Applicants have explained above how the primary references - even when combined with Jardines *et al.* or Earp *et al.* - don't describe therapy of a cancer which expresses EGFR and ErbB2, so this is one of the reasons claim 61 is considered patentable over the cited art.

Moreover, claim 61 is further distinguished over the cited art in that it entails administration of a therapeutically effective amount of an antibody which has the biological characteristics of monoclonal antibody 2C4 of (a) blocking HRG activation of an ErbB hetero-oligomer comprising ErbB2 and ErbB3 or ErbB4; and (b) binding to the ErbB2 epitope bound by monoclonal antibody 2C4. The cited art does not describe an antibody that blocks HRG activation of an ErbB hetero-oligomer comprising ErbB2 and ErbB3 or ErbB4, or an antibody that blocks binding of monoclonal antibody 2C4 to ErbB2, let alone therapy therewith as set forth in claim 61.

Hence, Applicants submit that claim 61 is patentable over the cited art.

Reconsideration and withdrawal of the Section 102 rejection based on Arakawa or Hudziak is respectfully requested.

SECTION 103

Claims 1, 2, 4-6, 8-9, 12-13, 16, 18-21, 24-29 and 61 are rejected under 35 USC Section 103 as being unpatentable over Greene *et al.*, or Arakawa *et al.* or Hudziak *et al.*, as evidenced by Jardines *et al.* or Earp *et al.* in view of Grim *et al. Am. J. Respir. Cell Mol. Biol.* 15: 348-354 (1996).

Applicants have demonstrated above how independent claims 1, 27 and 61 are patentable over the main references. Likewise, the claims which depend on those claims are patentable (certain dependent claims recite independently patentable features).

This Section 103 rejection includes claim 13 (to non-small cell lung cancer, NSCLC), claims 18-19 (to an antibody fragment, such as a Fab fragment in claim 19), claim 21 (an antibody fragment which is not conjugated with a cytotoxic agent), and claims 24-26 ("dosing" claims).

With respect to therapy as recited in claim 13, Applicants submit this is patentable over the cited art. The art does not disclose or suggest using an antibody that blocks binding of monoclonal antibody 2C4 to treat NSCLC - there is no evidence that the intracellular single-chain antibody in Grim blocks binding of 2C4 to ErbB2. Moreover, the cited art fails to describe therapy of NSCLC which expresses both EGFR and ErbB2 as in claim 13.

Claims 18-19 and 21 concerning therapy with antibody fragments that block binding of monoclonal antibody 2C4 to ErbB2 are also believed to be independently patentable over the cited art. The present application demonstrates that antibody fragments, *e.g.* Fab fragments, essentially retain the biological activity of the intact 2C4 antibody (see, *e.g.*, Figs. 6A-6B).

With respect to dosing claims 24-26, Applicants note that the Examiner has failed to explain where the art cited teaches the dosing therein.

Reconsideration and withdrawal of the Section 103 rejection is respectfully requested.

SECTION 112, FIRST PARAGRAPH

Claims 7 and 60 are rejected under 35 USC Section 112, first paragraph for lack of written description. The Examiner explains that the basis for the rejection is that the disclosure of monoclonal antibody 2C4 is not represenative of the

genus of antibodies that block TGF-alpha activation of MAPK.

Applicants submit that the specification provides a sufficient written description for the invention of claims 7 and 60 in order to satisfy the requirements of 35 USC Section 112, first paragraph.

Applicants submit that a consideration of the PTO's Written Description Guidelines, especially "Example 16: Antibodies" indicates that the specification satisfies the written description requirements with respect to claims 7 and 60.

A review of the full content of the specification indicates antibodies which bind to ErbB2 and block TGF-α activation of MAPK are essential to the invention in claims 7 and 60. The level of skill and knowledge in the art of antibodies at the time of filing was such that the production of antibodies against the well characterized ErbB2 antigen (page 7, lines 9-12 of the present application) was conventional and extensively described in the present application (pages 21-31 for instance). In 1999, when the present application was filed, this was a mature technology where the level of skill in the art was high and advanced. With respect to screening ErbB2 antibodies for their ability to block TGF-α activation of MAPK, the specification provides detailed guidance at pages 57-58, for instance.

Claim 7 recites the "method of claim 1 wherein the antibody blocks TGF-α activation of mitogen-activated protein kinase (MAPK)." Claim 60 recites "a method of treating cancer in a human, wherein the cancer expresses epidermal growth factor receptor (EGFR) and ErbB2, comprising administering to the human a therapeutically effective amount of an antibody which binds ErbB2 and blocks TGF-α activation of mitogen-activated protein kinase (MAPK)."

A search of the prior art by the Examiner has indicated that the invention set forth in claims 7 and 60 is novel and nonobvious (Applicants note that claims 7 and 60 were not rejected over prior art).

Considering the routine art-recognized method of making antibodies to the fully characterized ErbB2 antigen, and the detailed description in the present application of screening such antibodies for function as noted above, and the fact that the antibody technology was well developed and mature, one of skill in the art would have recognized that the spectrum of antibodies which bind to ErbB2 and have the function set forth in claims 7 and 60 were disclosed by the present

application.

With respect to Example 16 in the PTO's Written Description Guidelines, Applicants note that in the hypothetical given, there is no example of an antibody actually made in the application. In the present application, Applicants actually exemplify 2C4 including variants thereof (Example 3 on pages 53-57 describes humanized and affinity matured variants) which have the function set forth in claims 7 and 60. Hence, the specification provides several species which fall within the scope of the genus of antibodies encompassed by claims 7 and 60.

Applicants conclude that the disclosure meets the requirement under 35 USC Section 112, first paragraph as providing an adequate written description of the invention in claims 7 and 60.

Reconsideration and withdrawal of the Section 112, written description rejection of claims 7 and 60 is respectfully requested.

Applicants believe that this application is now in condition for allowance and look forward to early notification to that effect.

Respectfully submitted,
GENENTECH, INC.

Date: March 24, 2003

By: _____
Wendy Lee
Reg. No. 40,378
Telephone: (650) 225-1994

Serial No.: 09/602,812

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

61. (Amended) A method of treating cancer in a human, wherein the cancer expresses epidermal growth factor receptor (EGFR) and ErbB2, comprising administering to the human a therapeutically effective amount of an antibody which has [a] the biological characteristics of monoclonal antibody 2C4 of:
(a) blocking HRG activation of an ErbB hetero-oligomer comprising ErbB2 and ErbB3 or ErbB4; and
(b) binding to the ErbB2 epitope bound by monoclonal antibody 2C4.

Please add the following claim:

63. (New) A method of treating cancer in a human, wherein the cancer expresses epidermal growth factor receptor (EGFR) and ErbB2, comprising administering to the human a therapeutically effective amount of an antibody which binds to the ErbB2 epitope bound by monoclonal antibody 2C4.